REMARKS

The Examiner has rejected Claims 1, 2, 4, 6-11 and 13-15. The Examiner has withdrawn Claims 12, 16 and 17 as being drawn to a nonelected group (Group II and Group III), stating that there is no generic linking claim. Applicants have amended Claim 4 to recite the full name of the abbreviated surfactants and now present new Claims 18 – 23. Support for the new claims can be found throughout the specification and the originally filed claims (e.g., paragraphs 0010, 0016, 0020, 0029, 0029, 0039, and 0079). Accordingly, no new matter has been added by these amendments. Applicants now present Claims 1, 2, 4, 6-11, 13-15, and 18-23 for examination on the merits.

Rejection of Figures 6 and 9

The Examiner states that Figures 6 and 9 have graphs with no data disclosed on them and has required corrected drawings.

Applicants traverse this rejection on the grounds that the substitute sheets filed for Figures 6 and 9 during prosecution of the international application (PCT) contain sufficient data and information to allow one of skill in the art to discern the teachings set forth in the specification. That is, the substitute sheets filed during prosecution of the PCT application contain ample description to graphically represent the findings described in the specification. Accordingly, Applicants respectfully request that the rejections of Figures 6 and 9 be removed.

Objection to Claim 4

The Examiner has objected to Claim 4 for not having a full recitation of the acronyms used in the claim.

Applicants have amended Claim 4 to include the full recitation of each acronym, followed by the acronym in parenthesis. Applicants request removal of the objection to Claim 4.

Correction of minor errors in the Specification

Applicants have made a good faith effort to review the specification for any typographical errors. Applicants note that the title of the application was published with a typographical error made by the USPTO. Applicants sought correction through re-publication but the petition was

denied. Accordingly, to clarify any possible misunderstanding as to the proper title of the application, Applicants have amended the title to reflect the proper title that was filed with the application.

Rejections of Claims 8 and 10 under 35 USC § 112 first paragraph

The Examiner has rejected Claims 8 and 10 under 35 U.S.C. § 112 first paragraph for failing to comply with the enablement requirement. The Examiner states, "[t]he specification is not enabled for any vaccine comprising an antigenic component comprising an antigenic epitope from a virulent mycobacterium or for an improved vaccine for cancer, allergy or an autoimmune disease wherein the improvement comprises the adjuvant." (*Office Action* at page 3, paragraph 4).

Applicants respectfully submit that undue experimentation is not required to combine the presently claimed adjuvant with known vaccines for cancer, allergy, or autoimmune disease so as to achieve a formulation that elicits an improved immune response. Assays to determine whether such combinations produce an improved immune response are well known. That is, investigators routinely provide varying vaccine formulations containing a wide-range of adjuvants to animals and human beings and rapidly analyze whether such varied formulations improve antibody production and/or cellular responses to the antigen.

Applicants provide herewith a copy of a paper that demonstrates that the claimed adjuvant improves the immune response to a wide-range of antigens (*see Exhibit A*). The paper reports that the claimed adjuvant induced production of a strong immune response to *Mycobacterium, Chlamydia,* tetanus, and ovalbumin antigens (*See abstract and Figures 2, 3, 5, and 6).* As described in the originally filed specification, the presently claimed adjuvant improves the immune response to a wide range of antigens. Accordingly, Applicants respectfully request that the rejections of Claims 8 and 10 for lack of enablement be withdrawn.

Claim Rejections under 35 USC § 102 and §103

Claims 1, 4, 6-7, 10-11 and 13 have been rejected under 35 USC § 102 (b) as being anticipated by Liu et al. (U.S. Patent Application Publication No. 20020044951). Claims 1, 4, 6-11, 13 and 15 have also been rejected under 35 USC § 103(a) as being obvious in light of Liu and Andersen et al. (U.S. Patent Application Publication No. 20020176867) and Claims 1, 2 and 4 have further been rejected under 35 U.S.C. § 103(a) as being obvious in light of Liu et al. and Ravindranath et al. (U.S. Patent No. 6,218,166).

The Examiner argues that Liu et al. anticipates Claims 1, 4, 6-7, 10-11 and 13 because the reference teaches an adjuvant comprising DOTAP and an apolar fraction or part of a total lipid extract of a mycobacterium. The Examiner argues that Liu et al. and Anderson et al. make Claims 1, 4, 6-11, 13 and 15 obvious because one would incorporate the ESAT-6 and Ag85B antigens taught by Andersen et al. into the adjuvant taught by Liu et al. The Examiner further argues that Liu et al. and Ravindranath et al. makes Claims 1, 2, and 4 obvious because one would incorporate the phenolic glycolipids taught by Ravindranath et al. into the adjuvant taught by Liu et al.

Contrary to the Examiner's characterization of Liu et al., the reference does not teach an adjuvant "comprising" an apolar fraction or part of a total lipid extract of a mycobacterium. Liu et al. does not specifically disclose the particular combination of elements described by the Applicant. In paragraph [0031], Liu et al., discloses a long list of examples of non-peptide antigens from *M. tuberculosis* including fractionated non-peptide compounds and specific antigens; whereas, in paragraph [0049] Liu et al. discloses that the lipid antigens may be formulated into liposomes, which may comprise a phospholipid. DOTAP.Cl is one of 25 phospholipids mentioned.

While Liu et al., states that the lipid antigens can be formulated into liposomes with adjuvants such as QS-21 and that the liposomes may comprise phospholipids including carrier phospholipids, including DOTAP; Liu et al. specifically states that their vaccine compositions are made by sonicating and/or vortexing the phospholipid carrier and lipid antigen or at a minimum extruding the mixture through a filter of defined pore size (*see paragraph 0051).* Liu et al., further states that the "adjuvant" is then added after extrusion, i.e., after defined

phospholipid vesicles containing the lipid antigens and carrier phospholipids are formed (*Id.*). Accordingly, in the composition made by Liu et al., the adjuvant does not "comprise" the apolar fraction or part of a total lipid extract of mycobacterium, the lipid antigens are bound into phospholipids and the adjuvant is separate and apart from this structure. Applicants also note that the compositions described in Liu et al. do not contemplate the incorporation of DDA, DODA, or Dc Chol or additional tuberculosis antigens, such as ESAT6-Ag85B hybrid or a fragment thereof.

The Federal Circuit has recently reaffirmed prior Federal Circuit law ruling that it is improper to formulate an anticipation rejection by picking and choosing elements from various locations in the reference to arrive at the claimed invention. In *Net Moneyin, Inc. v. Verisign, Inc., et al.*, No. 2007-1565, U.S. Court of Appeals for the Federal Circuit, 10/20/2008; the Federal Circuit ruled in order to anticipate under 35 U.S.C. § 102 the prior art reference must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements "arranged as in the claim." *Id.*, p. 15, citing *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983). Accordingly, Applicants respectfully request that the rejections under 35 USC § 102 (b) be withdrawn.

Applicants also traverse the obviousness rejections raised by the Examiner on the grounds that Liu et al., does not teach an adjuvant "comprising" an apolar fraction or part of a total lipid extract of a mycobacterium and one of skill in the art would not combine either Andersen et al or Ravindranath et al. with Liu et al., because these references teach away from the combination and/or would not provide one of skill in the art with the requisite reasonable expectation of success at arriving at each and every limitation of the claims.

Applicant's first note that the discovery that a particular combination of surfactant and apolar fraction or part of a total lipid extract of a mycobacterium produced a synergistic immune response was surprising and unexpected. Table 1 of the specification shows that Ag85B-ESAT6 alone or combined with Ag85B-ESAT6/DDA are not capable of providing any notable protection against M. tuberculosis. In contrast, administration of a combination of Ag85B-ESAT6/DDA/apolar fraction of the total lipid extract of a mycobacterium produces a synergistic

immune response against M. tuberculosis. Similar results were also obtained when using the total lipid extract or the polar fraction of the total lipid extract; however, the immune response obtained when using the total lipid extract or the polar fraction was different from that obtained with the apolar fraction. The apolar fraction produced a much higher IFNγ response compared to that obtained when using the total lipid extract or the polar fraction. *(see* Table 7) and all of the extracts produced antibodies *(see* Table 8). Unexpectedly, Applicants found that the combination of surfactant and apolar fraction or part of a total lipid extract of a mycobacterium produced a potent adjuvant that can potentiate the immune response to a co-administered antigen.

As described above, Liu et al., only contemplates using the apolar fraction or part of a total lipid extract of a mycobacterium as an antigen in conjunction with other adjuvants and carrier phospholipids. Liu et al., prepares the compositions by sonicating/vortexing and extruding the preparation so as to create discretely sized liposomes, which are added to adjuvants. Liu et al. does not contemplate use of the apolar fraction or part of a total lipid extract of a mycobacterium and surfactant as the adjuvant *per se*.

While Andersen describes various antigenic components; for example, fusion proteins of the immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis, the inventors seek to develop potent single antigen vaccines (*see paragraph 0010),* specifically, the Ag85B-ESAT-6 fusion protein. Andersen et al. states that the 'in addition to being more cost-effective and less time consuming, the delivery of these selected molecules as a single fusion protein has the potential advantage of inducing amplified responses to molecules with a low inherent immunogenicity." (*see paragraph 0016)* . Accordingly, Andersen et al. teaches away from adding the ESAT-6 and Ag85B antigens into the milieu of antigens present in extracts as taught by Liu et al so as to arrive at the claimed invention.

Ravindranath et al., describes incorporating an adjuvant into or onto an intact cell. *(see column 3, lines 28-32*). Ravindranath et al., states that the use of whole cells is an important feature of the invention so as to insure that the antigens are presented in their natural environments and that any extraction method that removes the antigen from the membrane is likely to alter its immunogenic properties (*see column 4, lines 13-24).* Accordingly, Ravindranath et al., teaches away from applying the harsh conditions (i.e., sonication, vortexing,

and extrusion) employed by Liu et al. or the evaporation approach used by the applicants to arrive at the claimed invention. In light of the fact that Anderson et al. teaches away from applying a plurality of antigens in a vaccine formulation and Ravindranath et al. teach way from using approaches likely to disrupt the natural presentation of the antigen, as employed by Liu et al., Applicants respectfully submit that Liu et al. in combination with Anderson et al. and/or Ravindranath et al. do not render the claimed invention obvious. Applicants respectfully request that the rejections under 35 USC § 102 and §103 be withdrawn.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Conclusion

In view of the foregoing, Applicants submit that the application is in condition for allowance. If however, the Examiner believes that any additional issue remains or requires clarification, the Examiner is respectfully requested to call the agent of record in order to more expeditiously advance the examination of this application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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